PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 October 1998 (09.10.98)	
International application No. PCT/US98/03337	**Applicant's or agent's file reference** P1085R3
International filing date (day/month/year) 20 February 1998 (20.02.98)	**Priority date** (day/month/year) 21 February 1997 (21.02.97)
Applicant HSEI, Vanessa et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   11 September 1998 (11.09.98)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Col mbettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Maria Kirchner

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION T[illegible]

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECORDS ENT'D .....
RECORDS SEEN .....
DIARY ENT'D .....
[illegible]SNAL ENT'D X.....
[illegible]EADY ENT'D .....

PCT

To:

KIDDLE, Simon
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
GRANDE BRETAGNE

RECEIVED
25 JUN 1999

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)* 23.06.99	
Applicant's or agent's file reference SJK/FP5725635	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/03337	20/02/1998	21/02/1997

Applicant
GENENTECH, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/
European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0 Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer
Hingel, W
Tel.(+49-89) 2399-8717

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SJK/FP5725635		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/03337	20/02/1998	21/02/1997
International Patent Classification (IPC) or national classification and IPC		
C12N15/13		
Applicant		
GENENTECH, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11/09/1998	23.06.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Roscoe, R Telephone No. (+49-89) 2399 2554

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/03337

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-185 as originally filed

Claims, No.:

1-52 as received on 10/06/1999 with letter of 07/06/1999

Drawings, sheets:

1/136-136/136 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-52
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-52
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-52
	No:	Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

s separat sh et

1. Citations

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

2. Unity (Section IV)

The present application comprises two inventions, exemplified by claim groups 1-34 and 35-52. Search and examination fees have been paid for both.

3. Reasoned statement on Novelty, Inventive Step and Industrial Applicability (Section V)

3.1 Novelty (Art.33(2) PCT)

Invention group I (claims 1-34):

D2 discloses a wide range of conjugates including a PEGylated Fab-2 fragment of murine mAb A7 (p.99, l.20-21). The size of this conjugate is not disclosed, but reference to the cited Kitamura et al. (1990) paper shows that the average size of the conjugates in question was below 150 kDa. Hence, these conjugates do not anticipate the present claims.

The conjugate of D3 cannot anticipate the present claims since it comprises CPG_2 and is no larger than 300kDa.

D4 and D5 disclose PEGylated mAbs. Both involve full-length antibodies rather than antibody fragments, thus differing from the claimed conjugates. The size of the D4 conjugates is unknown. Those utilized in D5 would appear to be smaller than those claimed unless the peaks of digestion products relate to more than one fragment each. However, D5 discloses visible (i.e. very large) aggregates that were isolated and then disposed of (see p.179, col.1, bottom para.). These clearly exceeded 500 kDa in size.

D6 discloses PEGylated Fab' fragments, the sizes of which are approx. between 50 and 130 kDa. Thus D6 does not anticipate 500 kDa plus conjugates as claimed.

Invention group II (claims 35-52)

Novelty is acknowledged for claims 35-52, since the N35A/E mutations in light chain CDR1 render the claimed antibodies novel over those of D1.

3.2 Inventive Step (Art.33(3) PCT)

Invention group I (claims 1-34):

The critical question with regard to inventive step is the size of the conjugate(s). PEGylation of antibodies or fragments thereof is a common concept in the prior art. The nature of the specific antibody, or functional fragment thereof, chosen is merely a matter of routine choice and does not per se impart inventive activity. Applicant claims that his large PEGylated antibodies have unexpected properties in terms of increased serum half-life / residence time in circulation / reduced serum clearance rate (it is noted that these features are interrelated). Although it is already well known that PEG of increasing size can protect proteins against proteolysis and prevent systemic clearance (see D2, fig.3 (p.103)), the data suggests that little improvement can be expected once sizes of over 100 kDa have been reached. Table 10 in the application (p.141) shows that surprising further improvements in the level of serum clearance can be achieved by further increasing conjugate size.

Invention group II (claims 35-52):

The humanization of a known antibody is considered a routine procedure. Novelty is established by the additional N35A/E modification. Since, a higher affinity binding is surprisingly attributable to antibodies with this modification, which is not suggested in the prior art, inventivity can be acknowledged for claims 35-52.

3.3 Industrial Applicability (Art.33(4) PCT)

Claims 1-52 appear to have industrial applicability.

4. Certain observations (Section VIII)

4.1 Clarity (Art.6 PCT)

The terminology "consisting of one or more antibody fragments" technically can be interpreted as allowing a whole antibody (e.g. reconstituted from two fragments) bound to non-proteinaceous polymer to fall within the scope of the claim. This situation needs to be remedied, since the above interpretation potentially introduces a novelty-problem relating to documents D4 and D5. Since a skilled person would not refer to the description to understand such common terminology, and given that the description provides a suitable basis for introducing a clarifying definition into the claim (p.13, l.6-9), the definition used by the applicant should be introduced into the claim.

PATENT COOPERATION TREATY

PCT

09/355014

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
P1085R3		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 98/ 03337	20/02/1998	21/02/1997
Applicant		
GENENTECH, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [X] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. 66
   - [X] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/03337

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/13 C07K19/00 A61K47/48 C07K16/24 C12N15/85
C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 23865 A (GENENTECH, INC. & INDIANA UNIVERSITY FOUNDATION) 8 September 1995 see examples see claims ---	26-28, 35-52
A	N. KATRE: "The conjugation of proteins with polyethylene glycol and other polymers. Altering properties of proteins to enhance their therapeutic potential." ADVANCED DRUG DELIVERY REVIEWS, vol. 10, no. 1, 1993, pages 91-114, XP002084717 Amsterdam, The Netherlands see figure 3 --- -/--	1-25,29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 November 1998	04/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nooij, F

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	E. ENOAMOOQUAYE ET AL.: "Altered biodistribution of an antibody-enzyme conjugate modified with polyethylene-glycol." BRITISH JOURNAL OF CANCER, vol. 73, no. 11, June 1996, pages 1323-1327, XP002084718 London, GB see page 1324, left-hand column, line 33 - line 54 ---	1-25,29
A	E. MAINOLFI ET AL. 'REDUCTION OF IMMUNOGENICITY OF A MURINE ANTI-ICAM-1 ANTIBODY THROUGH PEGYLATION CHEMISTRY.': "In: THE 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY (abstract book), " July 1995 , SAN FRANCISCO, CA, USA XP002084720 see page 885, abstract 5247 ---	1-25,29
A	C. CUNNINGHAM-RUNDLES ET AL.: "Biological activities of polyethylene-glycol immunoglobulin conjugates." JOURNAL OF IMMUNOLOGICAL METHODS, vol. 152, no. 2, 10 August 1992, pages 177-190, XP000471626 Amsterdam, The Netherlands see 'Material and Methods' ---	1-25,29
A	C. DELGADO ET AL.: "Enhanced tumour specificity of an anti-carcinoembryonic antigen Fab' fragment by poly(ethylene glycol) (PEG) modification." BRITISH JOURNAL OF CANCER, vol. 73, no. 2, January 1996, pages 175-182, XP002084719 London, GB see the whole document -----	1-25,29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/03337

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9523865 A	08-09-1995	CA 2181787 A	08-09-1995
		EP 0749488 A	27-12-1996
		JP 9509837 T	07-10-1997
		US 5707622 A	13-01-1998
		US 5702946 A	30-12-1997
		US 5686070 A	11-11-1997
		US 5677426 A	14-10-1997

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SJK/FP5725635		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/03337	20/02/1998	21/02/1997
International Patent Classification (IPC) or national classification and IPC		
C12N15/13		
Applicant		
GENENTECH, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11/09/1998	23.06.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Roscoe, R Telephone No. (+49-89) 2399 2554

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/03337

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-185 as originally filed

Claims, No.:

1-52 as received on 10/06/1999 with letter of 07/06/1999

Drawings, sheets:

1/136-136/136 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-52
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-52
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-52
	No:	Claims

2. Citations and explanations

   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

s e separat sh t

1. Citations

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

2. Unity (Section IV)

The present application comprises two inventions, exemplified by claim groups 1-34 and 35-52. Search and examination fees have been paid for both.

3. Reasoned statement on Novelty, Inventive Step and Industrial Applicability (Section V)

3.1 Novelty (Art.33(2) PCT)

Invention group I (claims 1-34):

D2 discloses a wide range of conjugates including a PEGylated Fab-2 fragment of murine mAb A7 (p.99, l.20-21). The size of this conjugate is not disclosed, but reference to the cited Kitamura et al. (1990) paper shows that the average size of the conjugates in question was below 150 kDa. Hence, these conjugates do not anticipate the present claims.

The conjugate of D3 cannot anticipate the present claims since it comprises CPG_2 and is no larger than 300kDa.

D4 and D5 disclose PEGylated mAbs. Both involve full-length antibodies rather than antibody fragments, thus differing from the claimed conjugates. The size of the D4 conjugates is unknown. Those utilized in D5 would appear to be smaller than those claimed unless the peaks of digestion products relate to more than one fragment each. However, D5 discloses visible (i.e. very large) aggregates that were isolated and then disposed of (see p.179, col.1, bottom para.). These clearly exceeded 500 kDa in size.

D6 discloses PEGylated Fab' fragments, the sizes of which are approx. between 50 and 130 kDa. Thus D6 does not anticipate 500 kDa plus conjugates as claimed.

Invention group II (claims 35-52)

Novelty is acknowledged for claims 35-52, since the N35A/E mutations in light chain CDR1 render the claimed antibodies novel over those of D1.

3.2 Inventive Step (Art.33(3) PCT)

Invention group I (claims 1-34):

The critical question with regard to inventive step is the size of the conjugate(s). PEGylation of antibodies or fragments thereof is a common concept in the prior art. The nature of the specific antibody, or functional fragment thereof, chosen is merely a matter of routine choice and does not per se impart inventive activity. Applicant claims that his large PEGylated antibodies have unexpected properties in terms of increased serum half-life / residence time in circulation / reduced serum clearance rate (it is noted that these features are interrelated). Although it is already well known that PEG of increasing size can protect proteins against proteolysis and prevent systemic clearance (see D2, fig.3 (p.103)), the data suggests that little improvement can be expected once sizes of over 100 kDa have been reached. Table 10 in the application (p.141) shows that surprising further improvements in the level of serum clearance can be achieved by further increasing conjugate size.

Invention group II (claims 35-52):

The humanization of a known antibody is considered a routine procedure. Novelty is established by the additional N35A/E modification. Since, a higher affinity binding is surprisingly attributable to antibodies with this modification, which is not suggested in the prior art, inventivity can be acknowledged for claims 35-52.

3.3 Industrial Applicability (Art.33(4) PCT)

Claims 1-52 appear to have industrial applicability.

4. Certain observations (Section VIII)

4.1 Clarity (Art.6 PCT)

The terminology "consisting of one or more antibody fragments" technically can be interpreted as allowing a whole antibody (e.g. reconstituted from two fragments) bound to non-proteinaceous polymer to fall within the scope of the claim. This situation needs to be remedied, since the above interpretation potentially introduces a novelty-problem relating to documents D4 and D5. Since a skilled person would not refer to the description to understand such common terminology, and given that the description provides a suitable basis for introducing a clarifying definition into the claim (p.13, l.6-9), the definition used by the applicant should be introduced into the claim.

WE CLAIM:

1. A conjugate consisting essentially of one or more antibody fragments covalently attached to one or more nonproteinaceous polymer molecules, wherein the apparent size of the conjugate is at least about 500 kD.

2. The conjugate of claim 1, wherein the apparent size of the conjugate is at least about 800 kD.

3. The conjugate of claim 1, wherein the apparent size of the conjugate is at least about 1,400 kD.

4. The conjugate of claim 1, wherein the apparent size of the conjugate is at least about 1,800 kD.

5. The conjugate of claim 1, wherein the apparent size of the conjugate is at least ~~about~~ 8 fold greater than the apparent size of the antibody fragment.

6. The conjugate of claim 5, wherein the apparent size of the conjugate is at least ~~about~~ 15 fold greater than the apparent size of the antibody fragment.

7. The conjugate of claim 6, wherein the apparent size of the conjugate is at least ~~about~~ 25 fold greater than the apparent size of the antibody fragment.

8. The conjugate of claim 1, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv and $F(ab')_2$.

9. The conjugate of claim 8 wherein the antibody fragment is $F(ab')_2$.

10. The conjugate of claim 1 wherein the antibody fragment is covalently attached to no more than ~~about~~ 10 nonproteinaceous polymer molecules.

11. The conjugate of claim 10 wherein the antibody fragment is covalently attached to no more than ~~about~~ 5 nonproteinaceous polymer molecules.

12. The conjugate of claim 11 wherein the antibody fragment is covalently attached to no more than ~~about~~ 2 nonproteinaceous polymer molecules.

13. The conjugate of claim 12 wherein the antibody fragment is attached to no more than 1 nonproteinaceous polymer molecule.

14. The conjugate of claim 12, wherein the antibody fragment comprises a heavy chain and a light chain derived from a parental antibody, wherein in the parental antibody the heavy and light chains are covalently linked by a disulfide bond between a cysteine residue in the light chain and a cysteine residue in the heavy chain, wherein in the antibody fragment the cysteine residue in the light or heavy chain is substituted with another amino acid and the cysteine residue in the opposite chain is covalently linked to a nonproteinaceous polymer molecule.

15. The conjugate of claim 8 wherein the antibody fragment is selected from the group consisting of Fab, Fab' and Fab'-SH.

16. The conjugate of claim 15 wherein the antibody fragment is covalently attached to no more than 1 nonproteinaceous polymer molecule.

17. The conjugate of claim 16 wherein the nonproteinaceous polymer molecule in the conjugate is covalently attached to the hinge region of the antibody fragment.

18. The conjugate of claim 1 wherein the nonproteinaceous polymer is a polyethylene glycol (PEG).

19. The conjugate of claim 18 wherein the PEG has an average molecular weight of at least ~~about~~ 20 kD.

20. The conjugate of claim 19 wherein the PEG has an average molecular weight of at least ~~about~~ 40 kD.

21. The conjugate of claim 20 wherein the PEG is a single chain molecule.

22. The conjugate of claim 20 wherein the PEG is a branched chain molecule.

23. The conjugate of claim 19, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is a $F(ab')_2$ and is covalently attached to no more than ~~about~~ 2 PEG molecules.

24. The conjugate of claim 19, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is selected from the group consisting of Fab, Fab' and Fab'-SH and is covalently attached to no more than one PEG molecule.

25. The conjugate of claim 24 wherein the PEG molecule is covalently attached to the hinge region of the antibody fragment.

26. The conjugate of claim 1 wherein the antibody fragment has an antigen binding site that binds to human IL-8.

27. The conjugate of claim 26, wherein the conjugate contains no more than one antibody fragment, wherein the antibody fragment is selected from the group consisting of Fab, Fab' and Fab'-SH, wherein the antibody fragment is covalently attached to no more than one nonproteinaceous polymer molecule, and wherein the nonproteinaceous polymer molecule is a polyethylene glycol having an actual molecular weight of at least ~~about~~ 30 kD.

28. The conjugate of claim 1 wherein the antibody fragment is humanized.

29. The conjugate of claim 1 wherein the conjugate contains no more than one antibody fragment.

30. A composition comprising the conjugate of claim 1 and a carrier.

31. The composition of claim 30 that is sterile.

32. A conjugate formed by one or more antibody fragments covalently attached to one or more nonproteinaceous polymer molecules, wherein the apparent size of the conjugate is at least ~~about~~ 500 kD, and wherein the molecular structure of the conjugate is free of other matter.

33. A conjugate formed by one or more antibody fragments covalently attached to one or more nonproteinaceous polymer molecules, wherein the apparent size of the conjugate is at least ~~about~~ 500 kD, wherein the antibody fragment incorporates a nonproteinaceous label free of any polymer, and wherein the molecular structure of the conjugate is free of other matter.

34. The conjugate of claim 33 wherein the nonproteinaceous label is a radiolabel.

35. A polypeptide selected from the group consisting of: (1) a polypeptide that is an anti-IL-8 monoclonal antibody or antibody fragment comprising a light chain amino acid sequence comprising the complementarity determining regions of the light chain polypeptide amino acid sequence of Fig. 36; and (2) a polypeptide that is an anti-IL-8 monoclonal antibody or antibody fragment comprising a light chain amino acid sequence comprising the complementarity determining regions of the light chain polypeptide amino acid sequence of Fig. 45.

36. The polypeptide of claim 35, wherein the light chain amino acid sequence comprises the complementarity determining regions of the light chain polypeptide amino acid sequence of Fig. 45.

37. The polypeptide of claim 35 that further comprises a heavy chain amino acid sequence comprising the complementarity determining regions of the heavy chain polypeptide amino acid sequence of Figs. 37A-37B.

38. The polypeptide of claim 35 wherein the light chain amino acid sequence is selected from the group consisting of: (1) a light chain amino acid sequence comprising amino acids 1-219 of the light chain polypeptide amino acid sequence of Fig. 36; and (2) a light chain amino acid sequence comprising amino acids 1-219 of the light chain polypeptide amino acid sequence of Fig. 45.

39. The polypeptide of claim 38 wherein the light chain amino acid sequence comprises amino acids 1-219 of the light chain amino acid sequence of Fig. 45.

40. The polypeptide of claim 38 that further comprises a heavy chain amino acid sequence comprising amino acids 1-230 of the heavy chain polypeptide amino acid sequence of Figs. 37A-37B.

41. The polypeptide of claim 40, wherein the heavy chain amino acid sequence is fused at its C-terminus to a leucine zipper amino acid sequence.

42. The polypeptide of claim 41, wherein the leucine zipper sequence comprises amino acids 231-275 of the heavy chain polypeptide amino acid sequence of Figs. 37A-37B.

43. The polypeptide of claim 35 that is an antibody fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv and $F(ab')_2$.

44. The polypeptide of claim 38 that is a $F(ab')_2$ antibody fragment, wherein the antibody fragment comprises a first heavy chain amino acid sequence and a second heavy chain amino acid sequence each comprising amino acids 1-238 of the heavy chain polypeptide amino acid sequence of Figs. 37A-37B, and wherein each of the Cys residues at positions 231 and 234 in the first heavy chain amino acid sequence is in a disulfide linkage with the identical Cys residue in the second heavy chain amino acid sequence.

45. The polypeptide of claim 38 that is a Fab' or Fab'-SH antibody fragment, wherein the antibody fragment comprises a heavy chain amino acid sequence comprising amino acids 1-233 of the heavy chain polypeptide amino acid sequence of Fig. 53.

46. The polypeptide of claim 35 that is an antibody.

47. A nucleic acid molecule that comprises a nucleic acid sequence encoding the polypeptide of claim 35.

48. An expression vector comprising the nucleic acid molecule of claim 47 operably linked to control sequences recognized by a host cell transfected with the vector.

49. A host cell comprising the vector of claim 48.

50. A method of producing a polypeptide, comprising culturing the host cell of claim 49 under conditions wherein the nucleic acid sequence is expressed, thereby producing the polypeptide, and recovering the polypeptide from the host cell.

51. A composition comprising the polypeptide of claim 35 and a carrier.

52. The composition of claim 51 that is sterile.

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(71) Applicant *(for all designated States except US)*: GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080–4990 (US).

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(75) Inventors/Applicants *(for US only)*: HSEI, Vanessa [US/US]; 5047 Capistrano Avenue, San Jose, CA 95129 (US). KOUMENIS, Iphigenia [CY/US]; Apartment 6, 3820 Park Boulevard, Palo Alto, CA 94306 (US). LEONG, Steven, R. [US/US]; 1914 Eldorado Avenue, Berkeley, CA 94707 (US). PRESTA, Leonard, R. [US/US]; 1900 Gough Street #206, San Francisco, CA 94109 (US). SHAHROKH, Zahra [US/US]; 24 Sotelo Avenue, San Francisco, CA 94116 (US). ZAPATA, Gerardo, A. [US/US]; 785 Widgeon Street, Foster City, CA 94404 (US).

(74) Agents: LOVE, Richard, B. et al.; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080–4990 (US).

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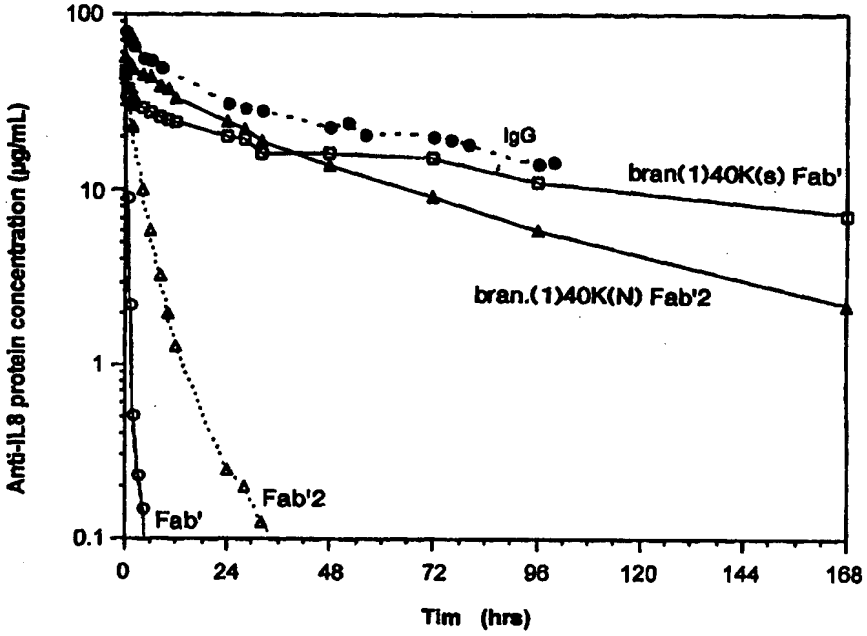
(54) Title: ANTIBODY FRAGMENT–POLYMER CONJUGATES AND HUMANIZED ANTI–IL–8 MONOCLONAL ANTIBODIES



(57) Abstract

Humanized anti–IL–8 monoclonal antibodies and variants thereof are described for use in diagnostic applications and in the treatment of inflammatory disorders. Also described is a conjugate formed by an antibody fragment covalently attached to a non–proteinaceous polymer, wherein the apparent size of the conjugate is at least about 500 kD. The conjugate exhibits substantially improved half–life, mean residence time, and/or clearance rate in circulation as compared to the underivatized parental antibody fragment.

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WE CLAIM:

1. A conjugate consisting essentially of one or more antibody fragments covalently attached to one or more nonproteinaceous polymer molecules, wherein the apparent size of the conjugate is at least about 500 kD.

2. The conjugate of claim 1, wherein the apparent size of the conjugate is at least about 800 kD.

3. The conjugate of claim 1, wherein the apparent size of the conjugate is at least about 1,400 kD.

4. The conjugate of claim 1, wherein the apparent size of the conjugate is at least about 1,800 kD.

5. The conjugate of claim 1, wherein the apparent size of the conjugate is at least about 8 fold greater than the apparent size of the antibody fragment.

6. The conjugate of claim 5, wherein the apparent size of the conjugate is at least about 15 fold greater than the apparent size of the antibody fragment.

7. The conjugate of claim 6, wherein the apparent size of the conjugate is at least about 25 fold greater than the apparent size of the antibody fragment.

8. The conjugate of claim 1, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv and $F(ab')_2$.

9. The conjugate of claim 8 wherein the antibody fragment is $F(ab')_2$.

10. The conjugate of claim 1 wherein the antibody fragment is covalently attached to no more than about 10 nonproteinaceous polymer molecules.

11. The conjugate of claim 10 wherein the antibody fragment is covalently attached to no more than about 5 nonproteinaceous polymer molecules.

12. The conjugate of claim 11 wherein the antibody fragment is covalently attached to no more than about 2 nonproteinaceous polymer molecules.

13. The conjugate of claim 12 wherein the antibody fragment is attached to no more than 1 nonproteinaceous polymer molecule.

14. The conjugate of claim 12, wherein the antibody fragment comprises a heavy chain and a light chain derived from a parental antibody, wherein in the parental antibody the heavy and light chains are covalently linked by a disulfide bond between a cysteine residue in the light chain and a cysteine residue in the heavy chain, wherein in the antibody fragment the cysteine residue in the light or heavy chain is substituted with another amino acid and the cysteine residue in the opposite chain is covalently linked to a nonproteinaceous polymer molecule.

15. The conjugate of claim 8 wherein the antibody fragment is selected from the group consisting of Fab, Fab' and Fab'-SH.

16. The conjugate of claim 15 wherein the antibody fragment is covalently attached to no more than 1 nonproteinaceous polymer molecule.

17. The conjugate of claim 16 wherein the nonproteinaceous polymer molecule in the conjugate is covalently attached to the hinge region of the antibody fragment.

18. The conjugate of claim 1 wherein the nonproteinaceous polymer is a polyethylene glycol (PEG).

19. The conjugate of claim 18 wherein the PEG has an average molecular weight of at least about 20 kD.

20. The conjugate of claim 19 wherein the PEG has an average molecular weight of at least about 40 kD.

21. The conjugate of claim 20 wherein the PEG is a single chain molecule.

22. The conjugate of claim 20 wherein the PEG is a branched chain molecule.

23. The conjugate of claim 19, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is a $F(ab')_2$ and is covalently attached to no more than about 2 PEG molecules.

24. The conjugate of claim 19, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is selected from the group consisting of Fab, Fab' and Fab'-SH and is covalently attached to no more than one PEG molecule.

25. The conjugate of claim 24 wherein the PEG molecule is covalently attached to the hinge region of the antibody fragment.

26. The conjugate of claim 1 wherein the antibody fragment has an antigen binding site that binds to human IL-8.

27. The conjugate of claim 26, wherein the conjugate contains no more than one antibody fragment, wherein the antibody fragment is selected from the group consisting of Fab, Fab' and Fab'-SH, wherein the antibody fragment is covalently attached to no more than one nonproteinaceous polymer molecule, and wherein the nonproteinaceous polymer molecule is a polyethylene glycol having an actual molecular weight of at least about 30 kD.

28. The conjugate of claim 1 wherein the antibody fragment is humanized.

29. The conjugate of claim 1 wherein the conjugate contains no more than one antibody fragment.

30. A composition comprising the conjugate of claim 1 and a carrier.

31. The composition of claim 30 that is sterile.

32. A conjugate formed by one or more antibody fragments covalently attached to one or more nonproteinaceous polymer molecules, wherein the apparent size of the conjugate is at least about 500 kD, and wherein the molecular structure of the conjugate is free of other matter.

33. A conjugate formed by one or more antibody fragments covalently attached to one or more nonproteinaceous polymer molecules, wherein the apparent size of the conjugate is at least about 500 kD, wherein the antibody fragment incorporates a nonproteinaceous label free of any polymer, and wherein the molecular structure of the conjugate is free of other matter.

34. The conjugate of claim 33 wherein the nonproteinaceous label is a radiolabel.

35. A polypeptide selected from the group consisting of: (1) a polypeptide that is an anti-IL-8 monoclonal antibody or antibody fragment comprising a light chain amino acid sequence comprising the complementarity determining regions of the light chain polypeptide amino acid sequence of Fig. 36; and (2) a polypeptide that is an anti-IL-8 monoclonal antibody or antibody fragment comprising a light chain amino acid sequence comprising the complementarity determining regions of the light chain polypeptide amino acid sequence of Fig. 45.

36. The polypeptide of claim 35, wherein the light chain amino acid sequence comprises the complementarity determining regions of the light chain polypeptide amino acid sequence of Fig. 45.

37. The polypeptide of claim 35 that further comprises a heavy chain amino acid sequence comprising the complementarity determining regions of the heavy chain polypeptide amino acid sequence of Figs. 37A-37B.

38. The polypeptide of claim 35 wherein the light chain amino acid sequence is selected from the group consisting of: (1) a light chain amino acid sequence comprising amino acids 1-219 of the light chain polypeptide amino acid sequence of Fig. 36; and (2) a light chain amino acid sequence comprising amino acids 1-219 of the light chain polypeptide amino acid sequence of Fig. 45.

39. The polypeptide of claim 38 wherein the light chain amino acid sequence comprises amino acids 1-219 of the light chain amino acid sequence of Fig. 45.

40. The polypeptide of claim 38 that further comprises a heavy chain amino acid sequence comprising amino acids 1-230 of the heavy chain polypeptide amino acid sequence of Figs. 37A-37B.

41. The polypeptide of claim 40, wherein the heavy chain amino acid sequence is fused at its C-terminus to a leucine zipper amino acid sequence.

42. The polypeptide of claim 41, wherein the leucine zipper sequence comprises amino acids 231-275 of the heavy chain polypeptide amino acid sequence of Figs. 37A-37B.

43. The polypeptide of claim 35 that is an antibody fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv and $F(ab')_2$.

44. The polypeptide of claim 38 that is a $F(ab')_2$ antibody fragment, wherein the antibody fragment comprises a first heavy chain amino acid sequence and a second heavy chain amino acid sequence each comprising amino acids 1-238 of the heavy chain polypeptide amino acid sequence of Figs. 37A-37B, and wherein each of the Cys residues at positions 231 and 234 in the first heavy chain amino acid sequence is in a disulfide linkage with the identical Cys residue in the second heavy chain amino acid sequence.

45. The polypeptide of claim 38 that is a Fab' or Fab'-SH antibody fragment, wherein the antibody fragment comprises a heavy chain amino acid sequence comprising amino acids 1-233 of the heavy chain polypeptide amino acid sequence of Fig. 53.

46. The polypeptide of claim 35 that is an antibody.

47. A nucleic acid molecule that comprises a nucleic acid sequence encoding the polypeptide of claim 35.

48. An expression vector comprising the nucleic acid molecule of claim 47 operably linked to control sequences recognized by a host cell transfected with the vector.

49. A host cell comprising the vector of claim 48.

50. A method of producing a polypeptide, comprising culturing the host cell of claim 49 under conditions wherein the nucleic acid sequence is expressed, thereby producing the polypeptide, and recovering the polypeptide from the host cell.

51. A composition comprising the polypeptide of claim 35 and a carrier.

52. The composition of claim 51 that is sterile.

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(71) Applicant *(for all designated States except US)*: GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080–4990 (US).

(72) Inventors; and

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(74) Agents: LOVE, Richard, B. et al.; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080–4990 (US).

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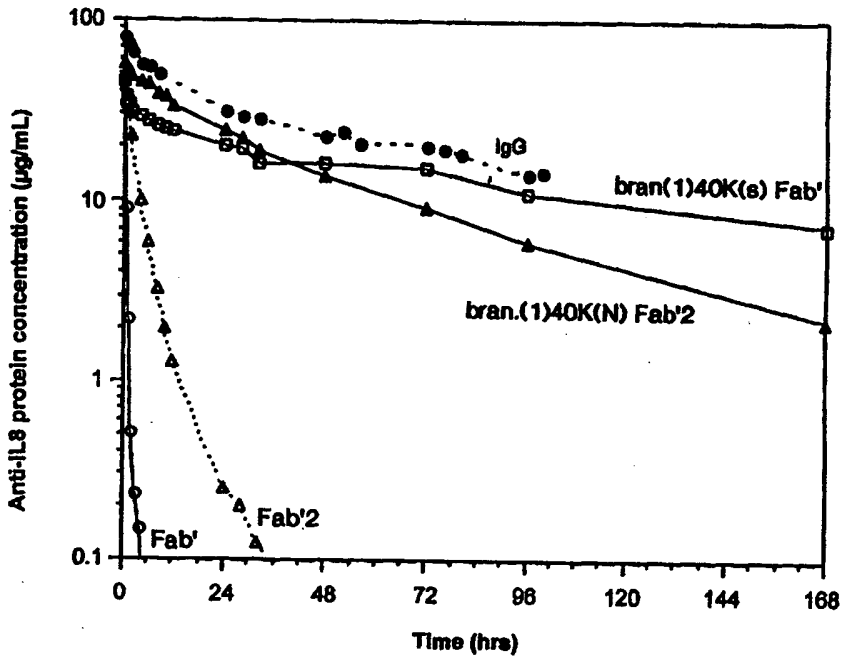

(57) Abstract

Humanized anti–IL–8 monoclonal antibodies and variants thereof are described for use in diagnostic applications and in the treatment of inflammatory disorders. Also described is a conjugate formed by an antibody fragment covalently attached to a non–proteinaceous polymer, wherein the apparent size of the conjugate is at least about 500 kD. The conjugate exhibits substantially improved half–life, mean residence time, and/or clearance rate in circulation as compared to the underivatized parental antibody fragment.

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/13 C07K19/00 A61K47/48 C07K16/24 C12N15/85
C12N5/10

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 23865 A (GENENTECH, INC. & INDIANA UNIVERSITY FOUNDATION) 8 September 1995 see examples see claims	26-28, 35-52
A	N. KATRE: "The conjugation of proteins with polyethylene glycol and other polymers. Altering properties of proteins to enhance their therapeutic potential." ADVANCED DRUG DELIVERY REVIEWS, vol. 10, no. 1, 1993, pages 91-114, XP002084717 Amsterdam, The Netherlands see figure 3	1-25,29

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17 November 1998	04/12/1998

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	E. ENOAMOOQUAYE ET AL.: "Altered biodistribution of an antibody-enzyme conjugate modified with polyethylene-glycol." BRITISH JOURNAL OF CANCER, vol. 73, no. 11, June 1996, pages 1323-1327, XP002084718 London, GB see page 1324, left-hand column, line 33 - line 54	1-25,29
A	E. MAINOLFI ET AL. 'REDUCTION OF IMMUNOGENICITY OF A MURINE ANTI-ICAM-1 ANTIBODY THROUGH PEGYLATION CHEMISTRY.': "In: THE 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY (abstract book), " July 1995 , SAN FRANCISCO, CA, USA XP002084720 see page 885, abstract 5247	1-25,29
A	C. CUNNINGHAM-RUNDLES ET AL.: "Biological activities of polyethylene-glycol immunoglobulin conjugates." JOURNAL OF IMMUNOLOGICAL METHODS, vol. 152, no. 2, 10 August 1992, pages 177-190, XP000471626 Amsterdam, The Netherlands see 'Material and Methods'	1-25,29
A	C. DELGADO ET AL.: "Enhanced tumour specificity of an anti-carcinoembryonic antigen Fab' fragment by poly(ethylene glycol) (PEG) modification." BRITISH JOURNAL OF CANCER, vol. 73, no. 2, January 1996, pages 175-182, XP002084719 London, GB see the whole document	1-25,29

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
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